Tetrahedron Letters No. 10, pp 883 - 886, 1978. Pergamon Press. Printed in Great Britain.

A SYNTHESIS OF γ-LACTONES BY REACTION OF LITHIUM β-LITHIOPROPIONATE WITH ALDEHYDES AND KETONES

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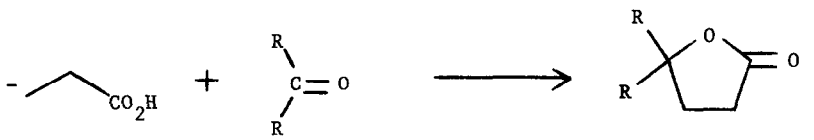
(Received in USA 16 December 1977; received in UK for publication 18 January 1978)

Several synthons of β-carboxy carbanions (1) have been added to aldehydes and/or ketones (2) and the products ultimately converted into γ-butyrolactones (3).[1] However, this methodology normally requires the use of complex reagents and/or several steps to elaborate the butanolide system. We wish to report a direct synthesis of γ-lactones which involves the addition of lithium β-lithiopropionate (4) to an aldehyde or ketone followed by lactonization of the γ-hydroxy acid adduct.



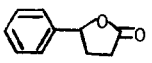
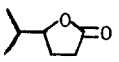
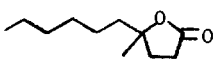
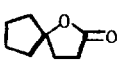
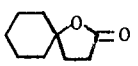
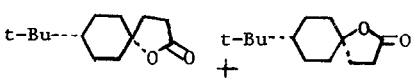
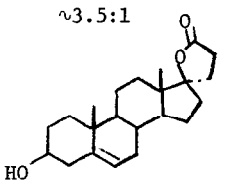
1 2 3

4 5

The β-lithio carboxylate 4 was prepared by first converting β-bromopropionic acid (5) into the corresponding lithium carboxylate with 1 equiv of n-butyllithium in tetrahydrofuran (THF) at low temperature and then adding the cold solution of the salt to a cold solution of lithium naphthalenide[2] in THF. Treatment of the resulting solution with the desired carbonyl compound, isolation of the acidic fraction of the reaction mixture, and lactonization of the γ-hydroxy acid product in THF containing a trace of p-toluenesulfonic acid gave the lactone. The results obtained using several representative carbonyl compounds are shown in the Table. All of the lactones prepared have been reported previously.

The preparation of 4 was attempted by reaction of 5 with 2.2 equiv of n-butyllithium in THF at -70 to -100° according to the procedure employed by Parham and coworkers[5] for the lithiation of

Table. Reaction of Aldehydes and Ketones with Approximately 1.5 Equiv.[a] of Lithium β-Lithiopropionate (4) in THF at -70°.

Carbonyl Component	Lactone	% Yield	Ref.
Benzaldehyde		56[b] (44)[c]	1a,3
Isobutyraldehyde		57[b] (43)[c]	1a
2-Octanone		53[b] (40)[c]	1b,1d
Cyclopentanone		35[b] (26)[c]	1a
Cyclohexanone		51[b] (41)[c]	1b,1d
4-t-Butyl-cyclohexanone	 ~3.5:1	58[b] (48)[c]	1b
Androst-5-en-3β-ol-17-one[d]		28[b] (66)[e]	4

a. In some runs approximately 3 equiv of 4 was employed without a substantial change in the yield. b. Isolated yield of product which was homogenous by nmr, ir, and glc. c. Yield of distilled product. d. The hydroxyl group was protected as the 2-methoxypropanyl derivative prior to reaction. e. Yield based upon unrecovered starting material.

bromoarylalkanoic acids. However, this apparently produced a very low yield of 4 because only a trace of lactone was isolated when cyclohexanone was added and the reaction mixture worked up as described above. The major product obtained was heptanoic acid which indicated that an unusually facile Wurtz coupling reaction[6] had occurred. The reaction of 5 with other organolithium compounds is being explored.

As shown in the Table, reaction of 4 with 4-t-butylcyclohexanone gave a ca. 3.5:1 mixture (by GLC) of the syn and anti spiro lactones[1b] derived from equatorial and axial addition, respectively, of the carbanionic reagent to the carbonyl group. Thus the stereochemistry of the addition of 4 is comparable to that observed for the reaction of other primary organolithium reagents with 4-t-butylcyclohexanone.[7] The reaction of 4 with the 2-methoxypropanyl derivative[8] of androst-5-en-3β-ol-17-one followed by lactonization provides a direct route to a steroidal spirolactone with the 17-oxygen atom β oriented.[4] Compounds of this type are aldosterone inhibitors.[4]

In the run involving the 17-keto steroid a large amount of starting material was recovered. This indicated that deprotonation of the ketone strongly competed with addition in this case. In the reactions involving the other carbonyl compounds only small amounts (less than 10%) of starting materials were recovered. In addition to the γ-hydroxy acids which underwent cyclization to the lactones, other acidic products were produced in all of the runs. The structures of these substances are under investigation.

The following provides a typical procedure using benzaldehyde as the carbonyl component. n-Butyllithium (10.40 ml of a 1.73 M solution in hexane) was added dropwise with stirring under nitrogen over ca. 30 min to a solution of 2.75 g (18 mmol) of 3-bromopropionic acid in 75 ml of anhydrous THF at -70°. While the temperature of the resulting lithium carboxylate solution was maintained at -70°, it was added dropwise with rapid stirring to a solution containing 30 mmol of lithium naphthalenide in 100 ml of anhydrous THF at -70° until the dark green color of the solution changed to dark brown. Benzaldehyde, 1.06 g (10 mmol), in 20 ml of anhydrous THF was then added dropwise with stirring while the temperature was maintained at -70°. The solution was held at -70° for 1 hr, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature.

The reaction mixture was then shaken with cold 5% sodium hydroxide and the layers were separated. The basic aqueous solution was washed with ether, cooled to ca. 5°, and neutralized with cold 15% hydrochloric acid. The resulting acidic materials were then isolated in the usual way and dissolved in 15 ml of anhydrous THF containing ca. 5 mg of p-toluenesulfonic acid and stirred overnight at room temperature. Diethyl ether (15 ml) was added and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried and the solvent was removed to give 0.910 g (56%) of a pale yellow oil. Distillation in a micro-Hickman still provided 0.710 g (44%) of γ-phenylbutyrolactone, b.p. 105-120° (bath temperature)/0.3 mm; m.p. 35-36°; reported[3] m.p. 37-38°.

Species such as 4 are homoenolates of carboxylates and exhibit "Umpolung"[9] (or polarity inversion[10]) of the normal electrophilic character of the β carbon of α,β-unsaturated carbonyl compounds. Therefore, we are investigating the reactions of 4 with other electrophilic reagents.

Acknowledgement - We are grateful to Professor Herbert O. House for many helpful discussions in connection with this work.

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